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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,873	09/30/2003	John Chan	COTH-P01-002	7993
28120	7590	10/16/2007		
ROPES & GRAY LLP PATENT DOCKETING 39/41 ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624			EXAMINER DEJONG, ERIC S	
			ART UNIT 1631	PAPER NUMBER
			MAIL DATE 10/16/2007	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/676,873

Applicant(s)

CHAN ET AL.

Examiner

Eric S. DeJong

Art Unit

1631

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 September 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 24 September 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☒ Applicant's reply has overcome the following rejection(s): see continuation sheet.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1,3-5,7-13,15,16,21-24,27-33,35 and 56.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s): \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

*Maynard D. Moroz*  
SPE, AU 1631  
10/15/07

EDJ  
10/11/2007

## Continuation of Item 5. NOTE:

The rejection of claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35 and 56 under 35 USC 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims filed 09/24/2007.

The rejection of claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35 and 56 under 35 USC 101 as being directed to non-statutory subject matter is withdrawn in view of amendments made to the instant claims filed 09/24/2007.

## Continuation of Item 11. NOTE:

The rejection of claims 1, 3-5, 7-13, 15, 16, 21-24, 27-33, 35 and 56 under 35 USC 112, first paragraph as failing to comply with the enablement requirement is maintained from the Final Office action mailed 03/23/2007.

In regards to the rejection of claims under 35 USC 112, first paragraph, applicants argue that the Office action continues to rely on a misinterpretation of Ginalski et al. Applicants argue that the over all sequence homology between the entire substituted recipient polypeptide and the entire wild-type polypeptide should be compared and not just the local sequence homology between the substituting (protease) motif and the substituted motif and that the key issue is what Ginalski et al. means by "very close (sequence) homology".

In response, it is first noted that the instant rejection is based on a full consideration of the 8 factors summarized by the CAFC. The basis of the instant rejection does not rely on Ginalski et al. alone, but further includes an analysis of the quantity of experimentation required necessary to practice the instant invention, the amount of guidance provided by the instant disclosure, the presence of working examples, the nature of the invention, the state of the prior art, the skill of those in the art, the predictability of the art, and the breadth of the instant claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable.

In the instant rejection, Ginalski et al. is relied upon for teaching that, absent the availability of very close homologs of known protein structures and wherein said homologs share high degrees of structural sequence, methods that provide for the reliable prediction of protein structure and activity are not known in the art (see Ginalski et al., page 1874, col. 1, line 15 through col. 2, line 5 and page 1887 col. 1, line 45 through col. 2, line 2). Ginalski et al. is further relied upon for teaching that current protein structure prediction methods is in its infancy (see Ginalski et al., page 1875, col. 2, lines 22-35). It is further agreed that the over all sequence homology between the entire substituted recipient polypeptide and the entire wild-type polypeptide should be compared, as argued by applicants. This is further supported by the teachings of Ginalski et al. However, the instant claims do not recite any limitation drawn to an assessment of sequence homology nor do the instant claims require any requisite level of sequence homology between the "spatially conserved motif" and the "recipient polypeptide" as instantly claimed. Therefore, applicants argument that the instant rejection relies upon on a misinterpretation of Ginalski et al. is not persuasive.

Applicants further provide a hypothetical example of proteins A and B with 94% sequence identity and argue that so long as the overall geometric shape of the conserved protease motif matches that of the to-be-replaced motif, the substituted polypeptide is expected to maintain the same three dimensional folding of the wild-type protein. Applicants further argue that when the overall geometric shape of the conserved protease motif matches that of the to-be-replaced motif, the substituted polypeptide is expected to maintain the same three dimensional folding of the wild-type protein. Applicants further argue that high sequence homology usually portends high structural similarity and that in the context of the claimed invention, and what is important is a matching structure between the protease motif and the to-be-replaced motif so that the overall structure of the substituted recipient polypeptide is conserved.

In regards to applicants hypothetical example, it is reiterated that the instant claims do not recite any limitation involving sequence homology between an entire substituted recipient polypeptide and an entire wild-type polypeptide, as set forth in applicants example, or between the "spatially conserved motif" and the "recipient polypeptide" as recited in the instant claims. Rather, the instant claims recite identifying a set of residues in a recipient polypeptide that matches a spatially conserved geometry of amino acids from a protease motif. As such, it is unclear how applicants hypothetical example is representative of the method recited in the instant claims.

It is also acknowledged that the instant claims do require the substitution of a protease motif into a generic recipient polypeptide, wherein the recipient polypeptide has an amino acid set that matches the geometric relation ship with said protease motif. However, the instant method considers only the spatial arrangement of amino acid residues in the recipient protein. The instant claims do not further address or consider how the alteration of the recipient polypeptide sequence to contain new amino acids residues (corresponding to said protease domain) will effect overall structure and activity of the real-world polypeptide. Ginalski et al. does address modeling techniques wherein a polypeptide sequence is modeled to match an existing or known structure (see Ginalski et al., page 1879, col. 1, line 33 through page 1880, col. 1, line 44). Regarding modeling and prediction approaches that fits a given sequence to a predicted structure, Ginalski et al. explicitly teaches:

"In the first approach... the surrounding structural environments for each residue of the query are kept identical to those observed in the template structure. This procedure is as fast as aligning a profile with a sequence but has important disadvantage that calculated in such a way local environments have little in common with those that might be observed in the native structure of the query protein. Most of them are essentially wrong, as majority of surrounding residues in template structure are replaced by different amino acids in the query protein."

This teaching from Ginalski et al. provides direct support that one of skill in the art would not be able to reliably predict what structure or activity, if any, a real-world engineered polypeptide sequence will actually possess, since the instant method of engineering relies only on modeling the spatial arrangement of amino acids between said protease domain and a set of native amino acids from the recipient polypeptide sequence. Therefore, it is maintained that a skilled practitioner would have to resort to trial and error experimentation in order to successfully engineer a recipient polypeptide so as to contain an active protease motif as instantly claimed. Such amounts to undue experimentation.